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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/817,913	LI ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-37 and 45-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-37 and 45-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Any rejection not reiterated in this Action is withdrawn.

Oath/Declaration-Rule 1.48(a) petition

Applicant's new declaration filed on September 30, 2004 is acknowledged. The submission states this new declaration is an accompaniment to a petition to correct inventorship under 37 CFR 1.48(a) filed on September 16, 2004. No petition with this date is present in the application file.

Claim Objections

Claim 45 is objected to because of the following informalities: the claim recites "a specific HDAC isoforms". Additionally, it is recommended that for the sake of clarity the abbreviation HDAC be written out at its first occurrence. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA

1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 34-36 and 45-49 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 20 of copending Application No. 09/563,728. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the claim of the co-pending application would be fully encompassed within the scope of the instant claims. Claim 20 of the copending application is directed to a species of the instant invention, a method of inhibiting histone deacetylase-I mediated neoplastic growth in a mammal using an antisense oligonucleotide that inhibits expression of histone deacetylase I. The claims of the instant invention are generic claims directed to use of any type of agent, including antisense oligonucleotides, directed to any isoform of histone deacetylase. The species claim of the copending application would thus anticipate the instant generic claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34 and 45-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Elements of the invention that are not adequately described by the specification include 1). the structure of histone deacetylase isoforms from all species encompassed by the instant claims, 2). representative structures of all types of inhibitor encompassed by the instant claims, 3). how to identify an inhibitor as one that will inhibit more than one histone deacetylase isoform but less than all histone deacetylase isoforms.

Claims 34 and 45 are directed to methods of inhibiting cell differentiation or proliferation, including neoplastic cell proliferation in an animal, by administering an agent that inhibits one or more specific histone deacetylase isoforms. Claim 35 limits claim 34 to inhibitors that are oligonucleotides complementary to a region of RNA or DNA that encodes a portion of one or more histone deacetylase isoforms while claim 36

limits the method to humans and claim 37 recites the further step of administering a small molecule inhibitor. Claims 46-48 limit claim 45 to neoplastic cell proliferation and recite specific histone deacetylase isoforms while claim 49 limits the method of claim 34 to humans. Claim 50 is directed to a method of inhibiting neoplastic cell proliferation in an animal by administering a small molecule inhibitor of histone deacetlyase. Claims 51 and 52 limit claim 50 to humans and the further step of administering an antisense oligonucleotide to histone deacetylase.

Claims 34, 45 and 50 are directed to methods that encompass inhibition of histone deacetylase isoforms from any species. The specification describes eight human histone deacetylase isoforms and the prior art describes various histone deacetylase structures from other species including murine and *Drosophila*. The structure of all histone deacetylase isoforms from all animal species is not disclosed in the specification or known in the prior art.

Claims 34 and 45 encompass the use of any inhibitor directed to any isoform of histone deacetylase from any species. Claim 50 is limited to the use of small molecule inhibitors. Inhibitors encompassed by claims 34 and 45 would include antisense oligonucleotides, ribozymes, proteins, antibodies, small organic molecules and inorganic molecules. The specification describes 17 antisense oligonucleotides directed to human histone deacetylase and three small molecule inhibitors. The specification does not describe and the prior art does not provide the structure of antisense oligonucleotides directed to histone deacetylase from species other than human, the structure of other types of nucleic acid inhibitors, the structure of protein or antibody

inhibitors or the structure of other small molecule inhibitors of histone deacetylase isoforms encompassed by the instant claims such that the full genus of inhibitors would be recognized as meeting the written description requirement.

The instant claims are directed to the use of inhibitors of histone deacetylase that are specific for one or more isoforms but less than all histone deacetylase isoforms. The specification does not describe what structure of the disclosed inhibitors provides the function of being an inhibitor of some isoforms but less than all isoforms such that one of skill in the art would recognize that an inhibitor would be functional against one isoform but not against all isoforms. Without such a disclosure, the skilled artisan would not be able to identify any particular inhibitor as one that will inhibit more than one specific histone deacetylase isoform but less than all histone deacetylase isoforms.

The skilled artisan cannot envision the detailed structure of the encompassed nucleic acid, protein, antibody and small molecule inhibitors directed to multiple isoforms of histone deacetylase from all species, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

Claims 34-37, 45-49 and 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition of histone deacetylase gene expression using nucleic acid modulators in cells *in vitro*, does not reasonably provide enablement for inhibition of histone deacetylase using antisense

oligonucleotides *in vivo* in a whole animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

The claims are directed to methods of inhibiting neoplastic cell proliferation in a cell or in an animal by administering alone or in combination agents that may be oligonucleotides or small molecules that inhibit one or more isoforms of histone deacetylase but less than all isoforms of histone deacetylase. Claims 34 and 52 are directed to inhibition within an animal and thus have only *in vivo* embodiments. Claims 45-49 are directed to modulation of cell proliferation or differentiation in a cell and thus have both *in vivo* and *in vitro* embodiments.

The specification describes antisense oligonucleotides targeted to human histone deacetylase and three small molecule inhibitors that inhibit histone deacetylase in cultured cells. The specification also describes one example using the disclosed small molecule inhibitors to inhibit tumor growth in mice.

The state of the prior art is such that inhibition of gene expression *in vitro* using nucleic acids is routine, but *in vivo* inhibition of gene expression at the time of filing and even to the present time is not routine for several reasons, including the problems of delivery, specificity and duration.

Problems related to therapeutic use of nucleic acids were well known in the art at the time of invention (see for example Agrawal et al. (Molecular Medicine Today, 2000, of record), Opalinska et al. (Nature Reviews Drug Discovery, 2002, vol. 1, p. 503-514) and Jen et al. (Stem Cells 2000, of record)). Such problems include the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect.

Jen et al. state (see page 313, second column, second paragraph)

> "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Opalinska et al. state on page 511

> "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all organisms, with a resultant inhibition of gene

expression, as claimed. The specification provides examples of inhibition of histone deacetylase using antisense oligonucleotides in cultured cells, however, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery of the exemplified cell line would not be applicable to delivery of oligonucleotides to any organism. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism). For example, Agrawal et al. (see p 79-80, section entitled "Cellular uptake facilitators for *in vitro* studies") states

> "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....*In vitro*, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide."

Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

Given these teachings, the skilled artisan would not know *a priori* whether introduction of antisense oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of expression of a target gene. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

Thus, while the specification is enabling for the examples set forth in the specification, the specification is not enabling for the broad claims of inhibiting the

expression of any isoform of histone deacetylase in any organism as the art of inhibiting gene expression by introducing antisense oligonucleotides into an organism is neither routine nor predictable. One of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 34-37, 45-49 and 52 are not enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 45-48 are rejected under 35 U.S.C. 102(b) as anticipated by Jones et al. (Nature Genetics, 1998, of record).

Claim 45 is directed to a method of modulating cell proliferation in a cell comprising the step of contacting the cell with an agent that inhibits one or more histone deacetlyase isoforms. Claims 46-48 limit claim 45 to proliferation that is neoplasia and recite specific histone deacetylase isoforms.

Jones et al. disclose contacting a cell with TSA, a small molecule inhibitor of histone deacetylase. Jones et al. do not explicitly state that proliferation of the cells is inhibited, but the method of Jones et al. comprises all of the steps of the claimed method and, absent evidence to the contrary, would be expected to inhibit proliferation, including neoplastic proliferation.

Thus, Jones et al. disclose all limitations of and anticipate claims 45-48.

Claims 34 and 45-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Kwon et al. (Proc. Natl. Acad. Sci. USA 1998, vol. 95, pages 3356-3361).

Claims 34 and 45 are directed to methods of inhibiting cell differentiation or proliferation, including neoplastic cell proliferation in an animal, by administering an agent that inhibits one or more specific histone deacetylase isoforms. Claims 46-48 limit claim 45 to neoplastic cell proliferation and recite specific histone deacetylase isoforms while claim 49 limits the method of claim 34 to humans. Claim 50 is directed to a method of inhibiting neoplastic cell proliferation by administering a histone deacetylase small molecule inhibitor, optionally to a human and optionally in combination with an antisense inhibitor.

Kwon et al. disclose a small molecule inhibitor which inhibits histone deacetylase-I, which has the effect of inducing the reversion of cells transformed with a known oncogene from the morphology of a transformed cell to that of a normal cell.

Thus, Kwon et al. disclose all limitations of and anticipate claims 34 and 45-51.

Claims 34-36 and 45-49 are rejected under 35 U.S.C. 102(e) as being anticipated by MacLeod et al. (US 2003/0078216).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claims 34 and 45 are directed to methods of inhibiting cell differentiation or proliferation, including neoplastic cell proliferation in an animal, by administering an agent that inhibits one or more specific histone deacetylase isoforms. Claim 35 limits claim 34 to inhibitors that are oligonucleotides complementary to a region of RNA or DNA that encodes a portion of one or more histone deacetylase isoforms while claim 36 limits the method to humans. Claims 46-48 limit claim 45 to neoplastic cell proliferation and recite specific histone deacetylase isoforms while claim 49 limits the method of claim 34 to humans.

MacLeod et al. disclose a method of inhibiting cell proliferation by inhibiting histone deacetlyase using antisense oligonucleotides. MacLeod et al. further disclose that the antisense oligonucleotides are targeted to the histone deacetylase isoforms recited in claim 47 and that the method may be performed in humans.

Thus, MacLeod et al. disclose all limitations of and anticipate claims 34-36 and 45-49.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 45-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sambucetti et al. (Journal of Biological Chemistry 1999, vol. 274, pages 34940-34947), Taunton et al. (Science 1996, cited on IDS), Baracchini et al. (US 5,801,154) and Bennett et al. (US 5,998,148).

Claim 45 are directed to methods of inhibiting cell differentiation or proliferation by administering an agent that inhibits one or more specific histone deacetylase

isoforms. Claims 46-48 limit claim 45 to neoplastic cell proliferation and recite specific histone deacetylase isoforms.

Sambucetti et al. teach that inhibition of histone deacetylase using the tetrapeptide inhibitor TPX inhibits tumor cell proliferation. Sambucetti et al. do not teach the use of antisense oligonucleotide inhibitors of histone deacetylase.

Taunton et al. teach the isolation and sequence of histone deacetylase-I.

Baracchini et al. teach that antisense oligonucleotides can be used for research purposes, and also teach that preferred antisense oligonucleotides are modified in their sugar, backbone linkage and nucleobase composition (col. 6). Baracchini teaches that such modifications are desirable in antisense oligos because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. Baracchini et al provide specific embodiments of such modifications at columns 6-8 and in Example 1. Tables 1-4 show the successful design and use of modified oligonucleotides in cells in culture. Table 1 exemplifies the successful practice of general antisense design taught at columns 8- 10. Column 4 teaches various carriers for antisense delivery. Baracchini et al. also teaches at column 8 that antisense oligonucleotides are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length. Baracchini is considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.

The teachings of Bennett et al. are considered to parallel those of Baracchini et al. Bennett et al. teaches general antisense targeting guidelines at columns 3-4.

Bennett et al. also teaches targeting 5'-untranslated regions, start codons, coding regions, and 3'-untranslated regions of a desired target. Bennett teaches, in column 5, for example, that antisense compounds are commonly used as research reagents and diagnostics. Column 5 indicates that antisense oligonucleotides 8-30 nucleotides in length are particularly preferred. Columns 6-7 teach that preferred antisense oligonucleotides contain modified internucleoside linkages including phosphorothioate linkages, among others. Columns 7-8 teach that preferred antisense oligonucleotides comprise modified sugar moieties including 2'-O-methoxyethyl. Bennett et al. also teach one of ordinary skill to modify nucleobases in antisense oligonucleotides, including the teaching of 5-methylcytosine (col. 8-9), and also to use chimeric antisense oligonucleotides (col. 9-10). Bennett et al. teach that the above modifications are known in the art to provide beneficial attributes to antisense oligonucleotides such as increased hybridization and nuclease protection, for example. Columns 10-24 teach numerous carriers for antisense oligonucleotides. Table 1 teaches the successful targeting of those regions taught in columns 3-4 with chimeric phosphorothioate oligonucleotides having 2'-MOE (a 2'-O-methoxyethyl modification). Thus, Bennett et al. is also considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.

It would have been obvious to one of ordinary skill in the art to use the cDNA sequence taught by Taunton et al. to generate antisense sequences as taught by Baracchini and Bennett for inhibition of histone deacetylase-I expression for the

purposes of treating neoplastic cells via inhibition of histone deacetylase-1 as taught by Sambucetti et al.

One would have been motivated to create such compounds because Sambucetti et al. teach that their inhibitor of histone deacetylase can be used to inhibit tumor cell proliferation. Furthermore, both Bennett and Baracchini et al. teach that antisense molecules can be easily made and used to inhibit any target so long as the sequence is known, and provide for their methods of use in humans. Therefore, one of ordinary skill in the art would have been motivated to use the sequence histone deacetylase of Taunton et al. to develop antisense inhibitors for the purpose of treating neoplastic cells, because Sambucetti et al. teach that inhibition of histone deacetylase-I can inhibit tumor cell proliferation.

Finally, one would have a reasonable expectation of success given that Baracchini et al. and Bennett et al. provide a detailed blueprint for making and using modified antisense compounds targeted to a target gene, the sequence of which is provided by Taunton, and the steps of which are routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention of claims 45-48 would have been prima facie obvious as a whole to one of ordinary skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The central FAX Number is 571-273-8300.

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Tracy Vivlemore
Examiner
Art Unit 1635

TV
December 16, 2005

J.D. SCHULTZ, PH.D.
PATENT EXAMINER